LEPTIN, HDL AND MATERNAL BMI ARE INDEPENDENT PREDICTORS OF OBESITY IN SCHOOL CHILDREN

Original Article

OKUL ÇOCUKLARINDA LEPTİN, HDL, MATERNAL BMI BAĞIMSIZ BELİRLEYİCİLERDİ

Hulya Ercan Saricoban

Yeditepe University, Faculty of Medicine, Department of Pediatrics, Istanbul, Turkey

Mustafa Berber

Yeditepe University, Faculty of Medicine, Department of Pediatrics, Istanbul, Turkey

Ahmet Ozen

Yeditepe University, Faculty of Medicine, Department of Pediatrics, Istanbul, Turkey

Hande Ozgun Karatepe

Yeditepe University, Faculty of Medicine, Department of Pediatrics, Istanbul, Turkey

Filiz Tiker Bakar

Yeditepe University, Faculty of Medicine, Department of Pediatrics, Istanbul, Turkey

Corresponding Author

Hülya Ercan Sarıçoban
Yeditepe Üniversitesi Hastanesi, Pediatri Bölümü Istanbul, Turkey
Tel: +90 216 5784000
Email: hulya_ercan@yahoo.com

ABSTRACT

Introduction: Dietary habits, lack of physical activity, parental obesity, parental education, and the socioeconomic level of the family have all been established as risk factors for childhood obesity. In a sample of elementary school children, we aimed to identify risk factors related to childhood obesity with an emphasis on the role of parental anthropometry, blood lipids, CRP and certain growth related molecules.

Materials and Methods: The study was carried out in four elementary schools in Istanbul.A questionnaire requesting sociodemographic information (age, family income, household crowding, breast feeding, parental anthropometrics) was given to be completed by the child's parents. At enrollment, body weight and height were recorded and BMI/BMI SDSs were calculated. The serum levels of total cholesterol, triglycerides, high and low density lipoprotein (HDL and LDL), C-reactive protein (CRP), eptin, ghrelin, and IGF-1 were measured.

Results: The study consisted of 620 (268 males,352 female) children with a mean age of 10.27±2.13years (min: 5.9 yrs, max: 15.3 yrs). Eighty-five children (13%) had obesity (>95th percentile). The rate of obesity was higher among males (17.2% versus 11.1%). Those children with obesity had significantly higher levels of CRP and leptin, whereas lower levels of HDL compared to those without. In the multivariate regression analysis, leptin ($p<0.0001$, OR: 4.84; 95%CI:0.029-0.070), HDL ($p=0.05$, OR: -1.94 95%CI: -0.021-0.00) and maternal BMI SDS ($p=0.006$, OR: 2.77; 95% CI: 0.06-0.35) were independent risk factors related to BMI SDS.

Conclusion: In a sample of elementary school children independent factors related to BMI SDS were leptin, HDL and maternal BMI. Determination of metabolic, genetic and environmental risk factors associated with obesity might help develop preventive strategies to this global health issue.

Key words: Childhood, obesity, risk factors, school children

ÖZET

Amaç: Çocukluk dönemi obesitesi için diyet alışkanlıkları, fiziksel aktivite azlığı, ailede abezite, ailenin eğitim düzeyi ve ailenin sosyoekonomik seviyesi risk faktörleridir. Orta okul dönemi okul çocuklarında obesite için risk faktörleri olduğu düşünülen parantel antropemetrik ölçüler, kan lipidleri, CRP ve büyüme ile ilişkili moleküllerin rolü araştırıldı.

Materyal ve Method: İstanbul'da bulunan dört orta okul öğrencileri çalışmaya dahil edildi. Çocukların ebeveynlerinden sosyoekonomik durumu değerlendiren bir anket (yaş, aile geliri, evde yaşayan kişi sayısı, anne sütü alımı, anne baba antropometrik ölçüleri) doldurmaları istendi. Vücut ağırlığı, boy, BMI/BMI SD hesaplandı. Serum tolal kolesterol, trigliserid, HDL, LDL, CRP, leptin, grelin ve IGF-1 değerleri ölçüldü.

Bulgular: Ortalama yaşları 10.27±2.13 yıl (min: 5.9 yıl, max: 15.3 yıl) olan (268 erkek, 352 kız) çocuk değerlendirildi. Elli beş (%13) çocuk obezdi (>95 %) . Obesite hızı erkeklerde yüksekti (% 17.2 iken %11.1). Obez çocukların CRP ve leptin düzeyleri istatistiksel anlamlı olarak yüksek ölçülürken, HDL sevileri düşük bulundu. BMI SD ile ilişkili faktörler ile multivariant regresyon analizi yapıldığında leptin ($p<0.0001$, OR: 4.84; 95%CI:0.029-0.070), HDL ($p=0.05$, OR: -1.94 95%CI: -0.021-0.00) ve anne BMI SDS ($p=0.006$,OR: 2.77; 95% CI: 0.06-0.35) bağımsız değişkenler olarak saptandı.

Sonuç: Ortaokul çağı çocuklarda BMI Sd yi etkileyen bağımsız faktörler leptin, HDL ve annelerinin BMI dir. Obezite gibi global sağlık sorununun önlenmesinde geliştirilen stratejilerde çocukların metabolic, genetic ve çevresel risk faktörleri belirlenmesi yardımcı olacaktır.

Anahtar kelimeler: çocukluk dönemi, obesite, risk faktörler, okul çocuğu

INTRODUCTION

Childhood obesity has become one of the most serious public health challenges of the 21st century. While the prevalence of obesity is higher in developednations, it is also in rise in the developing countries (1). According to the World Health Organization data (2006), approximately 155 million school-aged children are overweight or obese, worldwide (2). In a 2008 WHOsurvey, globally, over 40 million preschool children were found to be overweight (3). Overweight children are likely to become obese adults; have higher risk to develop diabetes and cardiovascular diseases at a younger age, which in turn pose risks for premature death and disability (3).

In Turkey, parallel to worldwidetrends, the prevalence of obesity and overweight is also increasing, at the levels of 3% and 20%, respectively (4). Various reports in Turkish children and adolescents indicate that its prevalence may also change from region to region (5-9). Obesity has been described as a multifactorial disorder influenced by genetic and non-genetic factors. Dietary habits, lack of physical activity, parental obesity, parental education, and the socioeconomic level of the family have been established as risk factors (3,7,10,11).

Childhood obesity is a strong predictor of adult obesity and an independent risk for cardiovascular and metabolic complications such as hyperlipidemia, hypertension(HT), atherosclerosis (AS), abnormal glucose tolerance, diabetes mellitus(DM), and infertility(12). Obese people tend to have high CRP, low HDL and high LDL, which are then risk factors for obesity-related diseases. (13,14).Globally, 44% of diabetes, 23% of ischemic heart disease and 7–41% of certain cancers are attributable to overweight and obesity (3).The prevention and treatment of obesity in children and adolescents may prevent or delay adult obesity and chronic diseases related to obesity (3).

Overweight and obesity are mostly assumed to be the result of increased caloric intake, which is why the neuroendocrine regulation of food intake plays an important role in obesity. Gut hormones such as ghrelin and leptin have been found to be important in appetite regulation (15). While leptin decreases appetite and increases the metabolic rate, ghrelin plays an antagonist role to leptin and stimulates hunger and food intake (16). It is thought that an imbalance between energy intake and expenditure plays role in the pathogenesis of obesity. Several recent studies have suggested a possible link between hypothalamic obesity and leptin, insulin, melatonin and endogenous cortisol hormones (17).

In this study we aimed to identify risk factors related to childhood obesity in a group of Turkish school children with a specific emphasis on the role of various biochemical and hormonal markers and also parental anthropometric measures. Identification of factors related to childhood obesity could help develop strategies for predicting children at risk and also develop preventive measures.

MATERIALS AND METHODS

Patients and questionnaire

The Ethics Committee of the Medical Faculty of Yeditepe University approved the study. Informed consent was obtained from the parents of each child. The selected schools, according to information obtained from Regional Education Offices, were representative of three income levels, as; low, middle and upper socioeconomic levels. Exclusion criteria included chronic systemic diseases that could potentially affect growth such as hepatic and renal diseases. In addition, children with Diabetes Mellitus necessitating insulin treatment and those children with height and weight below 2.5 standard deviation scores from the mean were also excluded from the study. Overall, a total of 620 children were evaluated with a mean age of 10.27±2.13years (min: 5.9 yrs, max: 15.3 yrs).

A questionnaire requesting sociodemographic information (age, family income, household crowding, breast feeding, parental anthropometrics) was given to the child's parents. At enrollment, the same researchers recorded body weight and height of the participating children. Weight was measured with an electronic scale and height with a conventional stadiometer. All measurements were performed with each child for ones. On the basis of normative data height, weight, BMI, midparental height (MPH), maternal BMI and paternal BMI were transformed to standard deviation scores (SDS) by using National Center for Health Statistics (NCHS) reference data according to age in one month intervals. BMI was calculated as weight divided by height squared (kg/m2). Measurements of triceps skin fold thickness (TSF) were made with a Holtain caliper (0.1 mm intervals) at the midpoint of the acromion-olecranon of the extended left arm. Waist and hip circumferences were measured at the narrowest area above the anterior iliac spine and widest area above the hip, respectively, in centimeters. On the basis of age and gender specific percentile curves children with BMI values higher than the 95th percentile for their age were evaluated as obese and those with values between the 5th and 95th percentiles as non-obese. The BMI values of the parents were calculated from the weight and height values reported by the parents. Parental obesity was defined as BMI value ≥30 kg/m2. A BMI value of 25-29.99 was defined as overweight; 18.5-24.99 as normal and <18.5 as underweight.

The economic status of the families was classified into three groups according to their annual income (low<500 $, middle 500-1500$, high≥1500 $). The minimum wage determined by the government was used as the cut-off point for the lowest income. Household crowding was categorized into two groups: five or fewer persons living in the same

household, and more than five persons. Breastfeeding was reported by the mothers in the questionnaire and categorizedinto three groups: breastfeeding for longer than 12 months, breastfeeding for up to 4-12 months, and breastfeeding for shorter than 4 months. The physical activity of the children was classified in six categories on the basis of nature, frequency and duration of the activity (regularly every day, irregular in the week, irregular in the weekend, regularly in the week, regularly in the weekend, performance player).

Samples and analytical method:

Measurement of Leptin, Ghrelin, IGF-I, CRP levels and fasting blood lipids.

The collection and handling of serum samples were performed according to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations and were frozen and stored at -80ºC until analysis. Within a maximum of 3 freeze-thaw cycles, each sample was tested twice for the Insulin-like growth factor 1 (IGF-1; DRG Instruments GmbH, Marburg, Germany) and Ghrelin (DRG International Inc., USA) using either sandwich or competitive commercial enzyme linked immunosorbent assays (ELISA). Principally, at the end of the color development reaction induced by a specific substrate, the concentrations of the correspondent analytes were either directly (for Leptin) or inversely proportional (for Ghrelin and IGF-1) to the intensity of the colors measured spectrophotometrically at the wavelength of 450 nm and quantitatively calculated using semi-logarithmic standard curves. The analytical sensitivities and maximal detection limits of the assays were; 0.1 ng/mL and 89 ng/mL for Leptin; 1.3 ng/mL and 600 ng/mL for IGF-1, and finally, 0.1 ng/mL and 100 ng/mL for Ghrelin, respectively, as determined by the manufacturers. The reference leptin and IGF-1 ranges were accepted to be 0.5-12.7 ng/mL for male and 3.9-30 ng/mL for female subjects; and 20-250 ng/mL for children aged 3-9 years and 130-600 ng/mL for subjects aged 10-16 years, respectively, whereas Ghrelin values of < 5 ng/mL were considered normal.

The serum total cholesterol, triglycerides (TG), high and low density lipoproteins (HDL and LDL) levels, all measured with enzymatic cholorimetric assays, as well as C-reactive protein (CRP) levels, measured with a turbidimetric assay, were developed according to International Federation of Clinical Chemistry (IFCC) recommendations and intended for use on the automatic COBAS INTEGRA 400 system for the quantitative determination of these analytes (Roche Diagnostics, GmbH, Mannheim, Germany). Very low density lipoprotein (VLDL; mg/dL) values were obtained by a calculation method using the Friedewald equation.

Statistical Methods

Results were presented as mean ± SD, median or number and percentage of children, as appropriate. Mann Whitney U-testand chi-square tests were used to determine the statistical significance of the differences between the two groups. Correlations between variables of interest were calculated using Pearson's coefficient of correlation. The level of statistical significance was set at $p< 0.05$. Statistical analysis was performed by the SPSS 13.0 (Chicago, IL USA) computer program.

The associations between obesity and growth parameters initially were investigated by simple statistical models. The growth parameters included height for age SDS, weight for age SDS, BMI SDS, waist to hip ratio (WTH), and TSF of the subjects. The significance of the associations was assessed by the t-test. The associations between obesity and BMI score with the biochemical parameters, which comprised ghrelin, leptin, IGF-1, total cholesterol, HDL, LDL, TG, VLDL and CRP levels, were analyzed multivariate regression analyses. Except for leptin and CRP, all other biochemical parameters were approximately

normally distributed and t-test was used to assess the significance of associations. The significance of the associations between obesity and leptin, ghrelin and CRP was estimated by the non-parametric Mann-Whitney U test. The relationship between obesity and family income, or household crowding was analyzed by the χ^2 test.

RESULTS

The demographic properties and characteristics of patients according to obesity are presented in Table 1. The study consisted of 620 (268 male, 352 female) children with a mean age of 10.27±2.13 years (min: 5.9 yrs, max: 15.3 yrs). The prevalence of obesity was found to be 13%, with a higher frequency in males (17.2% versus 11.1%).

Family related factors in obese and nonobese patients are shown in Table 2. Although statistically not significant, maternal obesity was more common among obese children than non-obese ones (16,9% vs. 10,8%). Analyses of the biochemical parameters revealed higher CRP and leptin levels and lower HDL in obese children as compared to those without (Table 3). Pearson correlation analyses revealed significant correlations between BMI SDS value and leptin (p<0.0001, r=0.29); IGF-1 (p=0.003, r=0.16);mac (p<0.0001, r=0.71); tsf (p<0.0001, r= 0.53); maternalBMI SDSs (p<0.0001, r=0.18); paternalBMI SDSs (p<0.0001, r=0.17); duration of breastfeeding (p=0.017, r=0.99); and serum levels of HDL (p=0.001,r= 0.18); triglycerides (p=0.001, r=0.18); and VLDL (p=0.01, r=0.18).

In the multivariateregression analysis taking BMI SDS as the dependent variable several factors were independently related; leptin (p<0.0001,OR: 4.84,95%CI: 0.029-0.070), HDL (p=0.05, OR: -1.94; 95% CI: -0.021-0.00) and maternal BMI SDS (p=0.006,OR: 2.77; 95% CI: 0.06-0.35)(Table 4).

	Obese (n=85)	**Non-obese (n=535)**	**p**
Age (years)	10.01(±2.05)	10.30 (±2.15)	0.343
BMI (kg/m²)	24.44(±3.02)	17.31(±2.39)	**<0.0001**
Number of persons in the family	4.47(±1.20) 4.00(4.00-5.00)	4.68(±1.24) 4.00(4.00-5.00)	0.068
Regular physical activity,n(%)	45(%57.7)	304(%59.6)	0.805
Duration of brestfeeding **<4 months** **4-12 months** **>12 months**	 20(%25.3) 26(%32.9) 33(%41.8)	 184(%36.9) 143(%28.7) 171(%34.3)	0.130

Table 1. Characteristics of the study group with regards to the obesity.

	Obese (n=85)	**Nonobese (n=535)**	**p**
MaternalBMI	26.32(±4.32)	25.22(±3.82)	0.059
PaternalBMI	26.94(±3.72)	26.08(±0.98)	0.061
MaternalBMI SDS	1.20(±0.89)	0.95(±0.92)	**0.025**
PaternalBMI SDS	1.26(±0.92)	1.04(±0.98)	0.064
Maternalheight	162.78(±6.20)	161.39(±6.64)	0.053
Paternalheight	173.01(±5.97)	172.67(±7.16)	0.736
Maternal BMI **<18.5** **18.5-24.99** **25-29.99** **≥30**	 1(%1.3) 34(%44.2) 29(%37.7) 13(%16.9)	 13(%2.8) 223(%48.0) 179(%38.5) 50(%10.8)	0.404
Paternal BMI **<18.5** **18.5-24.99** **25-29.99** **≥30**	 1(%1.3) 23(%29.9) 41(%53.2) 12(%15.6)	 10(%2.2) 181(38.9) 204(%43.9) 70(%15.1)	0.396
Father's education level	6(%7.1)	63(%12.0)	0.265
Family income(monthly) **low** **middle** **high**	 21(%11.4) 46(%14.3) 13(%15.9)	 164(%88.6) 275(%85.7) 69(%84.1)	0.523

Table 2. Characteristics of the families of study population

	Obese (n=85)	**Nonobese (n=535)**	**p**
Cholesterol mg/dl	158.48(±27.59)	160.76(±26.56)	0.595
Trigliserid mg/dl	90.87(±35.68)	82.59(±30.14)	0.175
HDL mg/dl	48.40(±11.20)	54.25(±13.53)	**0.006**
LDL mg/dl	91.89(±22.72)	89.91(±22.01)	0.578
VLDL mg/dl	18.16(±7.17)	16.56(±6.26)	0.185
Leptin ng/ml	8.38(±10.49)	3.06(±6.14)	**<0.0001**
Ghrelin ng/ml	2.06(±1.02)	2.03(±1.22)	0.440
IGF-1 ng/ml	183.86(±66.47)	184.38(±77.87)	0.758
CRP mg/L	2.24(±2.29)	1.62(±2.07)	**0.003**

Table 3. Biochemical parametersof the study group

	Univariate analysis			**Multivariate analysis**		
	p	OR	95% CI	p	OR	95% CI
Leptin ng/ml	**<0.0001**	**5.48**	**0.031-0.066**	**<0.0001**	**4.84**	**0.029-0.070**
IGF-1 ng/ml	**0.003**	**2.97**	**0.001-0.004**	0.096	1.67	0.000-0.003
CRP mg/L	0.47	0.72	-0.039-0.084			
Cholesterol mg/dl	0.92	-0.101	-0.005-0.005			
HDL mg/dl	**0.001**	**-3.28**	**-0.026-0.006**	**0.054**	**-1.94**	**-0.021-0.000**
LDL mg/dl	0.43	0.79	-0.004-0.008			
Trigliserid mg/dl	**0.001**	**3.25**	**0.003-0.011**	0.45	-0.76	-0.14-0.06
VLDL mg/dl	**0.001**	**3.44**	**0.015-0.054**	0.19	1.31	-0.008-0.042
Mean Family income	0.17	1.36	-0.045-0.29			
Sex	0.45	0.76	-0.12-0.26			
Age	0.52	0.64	-0.002-0.005			
Maternal BMI SDS	**<0.0001**	**4.39**	**0.13-0.34**	**0.006**	**2.77**	**0.06-0.35**
Paternal BMI SDS	**<0.0001**	**4.18**	**0.11-0.31**	0.12	1.58	-0.028-0.26
Duration of brestfeeding	**0.017**	**2.39**	**0.024-0.25**	0.58	0.56	-0.12-0.22

Table 4. Logistic Regression Analysis for factors predicting BMI SDS

DISCUSSION

In line with the trends in many geographies, the prevalence of obesity has increasedin our country, from 1.6% to 6.1%during the past few decades (18,19). Several factors have been identified as significant risks for obesity including physical inactivity, parental obesity, lower parental education and socioeconomic level in Turkish population (5-9). In the current study,13% of children were found to be obese,with predominance in males. Thisfigure is higher than previous population-based studies, probably reflecting the increased socioeconomic

level and changing dietary habits in our population.

The presence of obesity in the family, especially the parents, is a strong determinant of childhood obesity (18,19). It is well known that some families have a tendency towards obesity as a result of genetic predisposition (20).Meanwhile, shared dietary habits in the householdmight also play a causative role (10,21).It was shown that children with an obese mother or father or both have a four to five-fold increased risk for obesity(18.19).Our results confirmed the role of maternal obesityon the risk of theiroff springs; the higher the maternal BMI SDS the increased risk forthe child's obesity (OR: 2,77).Of note, no such relationshipwas found with paternal BMI.This biased association is likely related to the major role mothers play in the determination of dietary habits of their children as most of the women in this population are housewives, carrying the responsibility of preparing meals in the house. This finding is in line with a previous observation in our region, where 56% of obese adolescents had an obese family member, with the highest rates among mothers (7). Multivariate regression analysis revealed that leptin levels, HDL and maternal BMI SDS were independent factors influencing BMI SDSs. On the basis of these results, we suggest that preventive strategies against childhood obesity should take into account the dietary behaviors of children in the household. The feeding practices of mothers likely pose a major impact not only on the body habitus of their own but also on the shaping of their children's nutritional behavior throughout the growing period.

Of the environmental factors, which have an impact on body weight, nutrients are most influential. Within normal limits, hypothalamic and related neuronal populations correct perturbations in energy metabolism, to return the body to its nutritional set-point, either through direct response to nutrients or indirectly via peripheral appetite signals. Excessive intake of certain macronutrients, can lead to obesity and metabolic dysfunction. Appetite-related mediators, including circulating hormones, such as leptin and ghrelin, pro-inflammatory cytokines and the endocannabinoid intracellular messengers, are being examined for their potential role in mediating neurogenic responses to macronutrients (22,23). High leptin levels lead to a reduction in food intake and increased energy expenditure. Similar to previous data our results showed that plasma leptin levels are elevated in obese children, which is directly associated with adiposity (24-25).

In this study, obese children had a higher CRP and lower HDL levels than the non-obesecounterparts. Obesity has been associated with elevated levels of C-reactive protein (CRP), a marker of inflammation and predictor of cardiovascular risk (26, 27).Likewise, the rise in childhood obesity has lead to an increased number of children with lipid abnormalities and the predominance of a combined dyslipidemic pattern characterized by a moderate-to-severe elevation in triglycerides, normal-to-mild mild elevation in LDL cholesterol and reduced HDL cholesterol (28,29). All these lipid abnormalities are typical features of the metabolic syndrome and may be associated to a pro-inflammatory gradient which in part may originate in the adipose tissue itself and directly affect the endothelium (29).

A limitation to our study is the lack of dietary data, in terms of both the caloric intake and the nutritional composition. Secondly, although data was acquired on the physical activity levels of children by questionnaire direct quantitation of this activity could be more reliable. In addition, lack of the assesment of pubertal status might have confounded some results. Yet, we believe that our findings provide valuable information on the risk factors related to childhood obesity in the studied population. Analyses of various risk factors together enabled us to determine the combination of risk factors for obesity in this set of Turkish children.

In conclusion, we identified three independent factors related to the childhood obesity in a population of school children in Turkey; low HDL, high leptin and maternal adiposity. These factors should be taken into account in the preventive strategies directed towards childhood obesity.

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